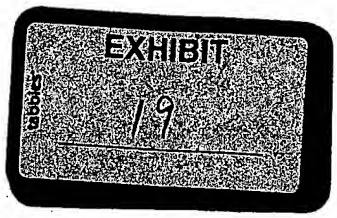

Alcohol 2002 May;27(1):63-8

Ethanol, oxidative stress, and cytokine-induced liver cell injury.

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Both clinical findings and results of experiments with animal models of alcoholic hepatitis have shown the importance of cytokine-mediated cell-cell interactions in the onset of ethanol-induced liver damage. Proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha), **interleukin (IL)-1 beta (IL-1 beta)**, and interleukin-6, are released from Kupffer cells or infiltrating neutrophils and macrophages and elicit defensive responses in parenchymal cells, including activation of apoptosis. Reactive oxygen species (ROS) and reactive nitrogen species (RNS), generated in response to cytokine-induced stress signals in parenchymal cells and also by activation of Kupffer cells and inflammatory cells, further mobilize cellular defense mechanisms. When these defensive responses are overwhelmed cells may die by necrosis, further stimulating inflammatory responses and infiltration of neutrophils. Chronic ethanol intake (i.e., many years of heavy alcohol use in human patients, several weeks or months in experimental animals) enhances the damaging consequences of these events through a variety of mechanisms. The formation of cytokines in the liver is stimulated by increasing circulating levels of endotoxin and by enhancing the responsiveness of Kupffer cells to such stimuli. In addition, ethanol promotes oxidative stress, both by increased formation of ROS and by depletion of oxidative defenses in the cell. Furthermore, liver cells from ethanol-treated animals are more susceptible to the cytotoxic effects of TNF-alpha and other cytokines than cells from control animals. Mitochondria play a critical role in the **apoptotic** response, and alterations in mitochondrial function after chronic ethanol treatment may contribute to enhanced cell death by apoptosis or necrosis. How the shift in the balance of cytokine-induced defensive and damage responses in hepatocytes contributes to the liver injury that occurs in alcoholic hepatitis remains poorly characterized and should be a rewarding area for future studies.